

1. A method of screening two-entity or higher order combinations for biological activity using at least seven entities in at least a seven-by-seven combinational array comprising at least forty-nine unique combinations of entities, said method comprising the steps of:

- Sub 1
- (a) providing said entities,
  - (b) creating said array of combinations of entities,
  - (c) providing a test element comprising one or more distinct biological moieties,
  - (d) contacting said array of combinations of entities with said test element under conditions that ensure that each entity/test element contacting is segregated from the others,
  - (e) detecting or measuring a property of the test element, and
  - (f) identifying combinations of entities that cause an effect on said property of the test element that is different from the effect of an entity of the combination by itself.

2. The method of claim 1, wherein steps (b) and (d) comprise sequentially contacting said entities with said test element, thereby creating said array in the presence of said test element.

3. The method of claim 1, wherein said test element comprises two or more distinct biological moieties.

4. The method of claim 3, wherein said test element comprises a living cell.

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5. The method of claim 4, wherein said detecting step (e) is performed by a cytoblot assay.

6. The method of claim 4, wherein said detecting step (e) is performed by a reporter gene assay.

7. The method of claim 4, wherein said detecting step (e) is performed by a fluorescence resonance energy transfer assay.

8. The method of claim 4, wherein said detecting step (e) is performed by detecting a fluorescent calcium-binding indicator dye.

9. The method of claim 4, wherein said detecting step (e) employs fluorescence microscopy.

10. The method of claim 4, wherein step (e) employs expression profiling.

11. The method of claim 4, wherein said cell is a human cell.

12. The method of claim 4, wherein said cell is selected from the group consisting of a cancer cell, an immune cell, a neuron, and a fibroblast.

13. The method of claim 1, wherein said test element comprises a cell-free medium comprising at least two organic biomolecules and at least one reporter molecule.

14. The method of claim 1, wherein one or both of steps (b) and (d) is carried out using a robotics system.

15. The method of claim 1, wherein one or both of steps (b) and (d) is carried out using microfluidics.

16. The method of claim 1, wherein one or both of steps (b) and (d) is carried out using ink-jet printer technology.

17. The method of claim 1, wherein said entities are compounds, ions, or radiation.

18. The method of claim 17, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

19. The method of claim 17, wherein said radiation is selected from the group consisting of visible light, light outside the visible range, and ionizing radiation.

20. The method of claim 1, wherein at least one of said entities is a compound employed in purified form.

21. The method of claim 20, wherein each of said compounds is employed in purified form.

22. The method of claim 1, wherein said entities are compounds provided as components of mixtures.

23. The method of claim 22, wherein said mixtures are natural product extracts.

24. The method of claim 1, wherein said effect is a synergistic effect.

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30. The method of claim 28, further comprising the step of (f) repeating step (a) through (e) at least twice, wherein, in step (a), said array of at least 200 combinations is different in each repetition.

31. The method of claim 30, wherein at least two repetitions of step (f) occur within 10 days of each other.

32. The method of claim 28, wherein said array comprises at least 400 unique combinations.

33. The method of claim 28, wherein said array comprises at least 1540 unique combinations.

34. The method of claim 28, wherein said entities are compounds, ions, or radiation.

35. The method of claim 34, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

36. The method of claim 34, wherein said radiation is selected from the group consisting of visible light, light outside the visible range, and ionizing radiation.

37. The method of claim 28, wherein at least one of said entities is a compound employed in purified form.

38. The method of claim 28, wherein each of said compounds is employed in purified form.

39. The method of claim 28, wherein said entities are compounds provided as components of mixtures.

40. The method of claim 38, wherein said mixtures are natural product extracts.

41. The method of claim 28, wherein said effect is a synergistic effect.

42. The method of claim 28, wherein one or both of steps (a) and (c) is carried out using a robotics system.

43. The method of claim 28, wherein one or both of steps (a) and (c) is carried out using microfluidics.

44. The method of claim 28, wherein one or both of steps (a) and (c) is carried out using ink-jet printer technology.

45. A method of treating a patient comprising administering to said patient a combination identified according to the method of claim 28.

46. A combination of entities identified according to the method of claim 28.

47. A pharmaceutical composition comprising (i) a combination of entities identified according to the method of claim 28, and (ii) a pharmaceutically acceptable carrier.

48. A method for screening two-entity or higher combinations for biological activity, said method comprising the steps of:

- Sub 29
- (a) creating an array of at least 49 unique two-entity or higher order combinations,
  - (b) providing a test element comprising one or more distinct biological moieties,
  - (c) contacting said array of combinations of entities with said test element under conditions that ensure that each entity/test element contacting is segregated from the others,
  - (d) detecting or measuring a property of the test element,
  - (e) identifying combinations of entities that cause an effect on said property of the test element that is different from the effect of an entity of the combination by itself, and
  - (f) repeating steps (a) through (e) at least 25 times over a one week period, using a different array in each repetition.

49. The method of claim 48, wherein steps (a) through (e) are repeated at least 100 times over a 30-day period, using a different array in each repetition.

50. The method of claim 48, wherein said entities are compounds, ions, or radiation.

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51. The method of claim 50, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

52. The method of claim 50, wherein said radiation is selected from the group consisting of visible light, light outside the visible range, and ionizing radiation.

53. The method of claim 48, wherein said entities are compounds employed in purified form.

54. The method of claim 48, wherein said entities are compounds provided as components of mixtures.

55. The method of claim 54, wherein said mixtures are natural product extracts.

56. The method of claim 48, wherein said effect is a synergistic effect.

57. The method of claim 48, wherein one or both of steps (a) and (c) is carried out using a robotics system.

58. The method of claim 48, wherein one or both of steps (a) and (c) is carried out using microfluidics.

59. The method of claim 48, wherein one or both of steps (a) and (c) is carried out using ink-jet printer technology.

60. A method for screening two-entity or higher order combinations for biological activity, said method comprising the steps of:

- (a) creating an array of at least 10,000 unique two-entity or higher order combinations from a set of entities,
- (b) providing a test element comprising one or more distinct biological moieties,
- (c) contacting said array of combinations of entities with said test element under conditions that ensure that each entity/test element contacting is segregated from the others,



- (d) detecting or measuring a property of the test element,
- (e) identifying combinations of entities that cause an effect on said property of the test element that is different from the effect of an entity of the combination by itself, and
- (f) repeating steps (a) through (e) at least twice over a period of ten days or less, wherein, in step (a), said array of at least 10,000 two-entity combinations is different in two or more repetitions.

61. A method for screening combinations of entities for biological activity, said method comprising the steps of:

- (a) providing a test element comprising one or more distinct biological moieties,
- (b) contacting said test element with at least 100 entities under conditions that ensure that each entity/test element contacting is segregated from the others,
- (c) detecting or measuring a property of said test element,
- (d) selecting entities that cause a change in said property relative to said property of said test element not contacted with said entities,
- (e) creating an array of at least 49 unique two-entity or higher order combinations from the identified entities,
- (f) contacting said array of combinations of entities with a test element under conditions that ensure that each entity combination/test element contacting is segregated from the others,
- (g) detecting or measuring a property of the test element of step (f), and
- (h) identifying combinations of entities that cause an effect on said property of step (g) that is different from the effect of an entity of the combination by itself.

62. The method of claim 61, wherein the test element of step (a) is the same as the test element of step (f).



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